



# UNITED STATES PATENT AND TRADEMARK OFFICE

AK

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,854	07/23/2003	Andre Delacourte	11362.0039.NPUS01	9442

23369 7590 02/07/2006

HOWREY LLP  
C/O IP DOCKETING DEPARTMENT  
2941 FAIRVIEW PARK DRIVE, SUITE 200  
FALLS CHURCH, VA 22042-7195

EXAMINER
----------

WANG, CHANG YU

ART UNIT	PAPER NUMBER
----------	--------------

1649

DATE MAILED: 02/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/625,854	<b>Applicant(s)</b> DELACOURTE ET AL.	
	<b>Examiner</b> Chang-Yu Wang	<b>Art Unit</b> 1649	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on January 12, 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 26 and 29-54 is/are pending in the application.
- 4a) Of the above claim(s) 38 and 44-54 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 26, 29-37 and 39-43 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>06/10/04</u> .  | 6) <input type="checkbox"/> Other: _____                                    |

## DETAILED ACTION

### ***Status of Application/ Election/Restrictions***

1. Applicant's election with traverse of Group I and N-terminal truncated/post-translationally modified  $\beta$ -amyloid variant, A peptide, and species of start position 4, methylation at position 4,  $A\beta$  (4-42), and  $A\beta$  (5-42) in the reply filed on January 16, 2006 is acknowledged. The traversal is on the ground(s) that the method of screening clearance of  $\beta$ -amyloid in the Group II is complementary to the method of determining the susceptibility to a disease associated with  $\beta$ -amyloid formation/aggregation in the Group I. The potential mechanisms for the  $A\beta$  clearance could be through the formation a complex of ApoE or  $\alpha$ 2-M with  $A\beta$  and endocytosis of the  $A\beta$ /ApoE or  $A\beta$ / $\alpha$ 2-M complex by LDL-receptor related protein (LRP), or an immune response of glial cells. In addition,  $\gamma$ -secretase, presenilin, and notch have been demonstrated involved in processing APP and generation of  $A\beta$ . Therefore, a method for determining whether a person susceptible to a disease associated with  $A\beta$  formation/aggregation can be achieved by detecting the genes involved in the process of APP and generation of  $A\beta$  at the gene, transcription, translation or posttranslational level with different means, such as proteomics, immunological, RT-PCR or genetic markers approaches. However, Applicant's argument has been fully considered and found persuasive. Therefore, Group II is rejoined to Group I and included in this examination. However, with regard to the traverse of rejoining Group III together with Groups I and II is not found persuasive because the method of determining the susceptibility to a disease

Art Unit: 1649

associated with A $\beta$  formation or screening the clearance of A $\beta$  does not necessarily require the product in the Group III. Therefore, Group III is patentably distinct from Groups I and II.

2. The requirement for the rest of the restrictions is still deemed proper and is therefore made FINAL.

3. Claims 26 and 29-54 are pending. Claims 38 and 44-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group III, there being no allowable generic or linking claim. In addition, claim 37 is also withdrawn from further consideration because of non-elected species. Claims 26, 29-36 and 39-43 are under examination in this office action

#### ***Priority***

4. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

#### ***Information Disclosure Statement***

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a

Art Unit: 1649

separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

### ***Claim Objections***

6. Claims 31-36 and 43 are objected to as encompassing non-elected subject matter.

### ***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 26, 29-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

9. "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;

- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

10. The claims are drawn to a method for determining whether a mammal is susceptible to a disease associated with  $\beta$ -amyloid formation and a method for screening the clearance of A $\beta$  deposition in a mammal comprising comparing the amount of N-terminal truncated/post-translationally modified  $\beta$ -amyloid variant in the said mammal with a control. The specification discloses that there is an increase of N-terminal truncated A $\beta$  peptides in extracts derived from brain tissues of patients who died of Alzheimer's disease (AD) and animal models by using 2D electrophoresis and detecting immunoblots with anti-N-terminal A $\beta$  antibodies, 6E10 (recognizes residues 4-13 of A $\beta$ ) and WO2 (recognizes residues 5-8 of A $\beta$ ), and anti-C-terminal A $\beta$  antibodies, 21F12 and ADA40. Applicant also discloses that the increase of N-terminal truncated A $\beta$  can be post-translationally modified by methylation and pyroglutamylation by mass spec analysis. Further, Applicant discloses that the increase of N-terminal truncated A $\beta$  can be detected in the CSF derived from AD patients. However, Applicant fails to teach

Art Unit: 1649

how to identify a mammal susceptible to or at risk to develop a disease associated with A $\beta$  formation/aggregation by detecting these modifications. Applicant also fails to teach how to screen the clearance of A $\beta$  or predict the level of A $\beta$  burden using these modifications. The disclosures provided by Applicant have not taught how N-terminal truncated A $\beta$ /post-translationally modified A $\beta$  variant is related to the clearance of A $\beta$  or A $\beta$  burden in a mammal. The prior art has proposed that the clearance of A $\beta$  may be through the mechanisms of receptor-mediated endocytosis of the complex of ApoE or  $\alpha$ 2-M with A $\beta$  by LDL-receptor related protein (LRP) or receptor for advanced glycation end products (RAGE). The clearance of A $\beta$  may be also through the mechanisms of degradation of A $\beta$  by Zinc metalloendopeptidases, insulin degrading enzyme (IDE or insulysin) or neprilysin (NEP), or may through the immune response of glial cells to generate anti-A $\beta$  antibodies (Tanzi et al. Neuron 2004. 43: 605-608). However, Applicant has not provided any guidance of the correlation between the level of prediction for a disease associated with A $\beta$  formation and the level of detection. The prior art has demonstrated that  $\gamma$ -secretase and presenilin are involved in processing APP and generation of A $\beta$  (Hardy et al. Science 2002. 297: 353-356). Each one of the molecules mentioned above has a potential to affect the clearance or generation of A $\beta$ . Besides, the generation and clearance of A $\beta$  are naturally physiological processes. Therefore, it is difficult to envision what level and what kind of N-terminal truncated A $\beta$  can be considered as abnormal and thus is an A $\beta$  burden for disease or at risk to develop the disease associated with A $\beta$  formation/aggregation. In addition, Applicant

Art Unit: 1649

only described some members of the genus of the N-terminal truncated A $\beta$  or post-translationally modified A $\beta$  variants, thus the skilled artisan cannot envision what others species of N-terminal truncated or post-translationally modified A $\beta$  variants to detect. Furthermore, every one of us is at risk of developing a disease associated A $\beta$  formation/aggregation, however, Applicant has not provided any specific information to predict which one of us would develop a disease associated with A $\beta$  formation/aggregation or which one of us would not based on the claimed method. The specification has not taught what would be different in normal people and people at risk for AD in what level of A $\beta$  since the clearance of A $\beta$  occurs naturally in any persons with any conditions. The specification has not taught what level of A $\beta$  is considered as an A $\beta$  burden and what level of A $\beta$  can be considered as free of an A $\beta$  burden. Since the specification has provided no information as to how to predict the level of A $\beta$  burden, screen the clearance of A $\beta$  and to predict what person would develop a disease associated with A $\beta$  formation/aggregation, undue experimentation is required for a person of skill in the art to use the invention.

11. Claims 30 and 39 are further rejected because Applicant fails to disclose how to distinguish the naturally occurring N-terminal truncated A $\beta$  from the exogenous while administering exogenous N-terminal truncated A $\beta$  in a mammal and comparing the amount of N-terminal truncated A $\beta$  from the said mammal with that in a control. Further, Applicant has not provided enough guidance as to whether all N-terminal truncated A $\beta$



are immunogenic and able to elicit an immune response. Moreover, although it has been disclosed that most AD patients develop anti-A $\beta$  autoantibodies, these anti-A $\beta$  autoantibodies have not been well characterized. It has been speculated that these autoantibodies may help clear A $\beta$  in normal persons (Tanzi et al. Neuron 2004. 43: 605-608). Applicant fails to teach how much increased amount of antibody or reactive T-cells specific for N-terminal truncated A $\beta$  in a mammal can be considered as at risk to develop a disease associated with A $\beta$ -formation/aggregation. Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention. Without such guidance, whether the N-terminal truncated is distinguishable from endogenous A $\beta$  is unpredictable, indicating that undue experimentation is required for those skilled in the art to practice the invention.

12. Thus, in view of the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would require more undue experimentation to practice the claimed invention.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 26, 29, 31-36, 40-43 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the controls.

***Conclusion***

NO CLAIM IS ALLOWED.

15. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

16. Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Art Unit: 1649

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW

January 27, 2006

  
JANET L. ANDRES  
SUPERVISORY PATENT EXAMINER